REMARKS

In this response to the Office Action dated March 19, 2009, Applicants have amended claims 18, 20, 21, 25, and 28, and added new claims 32 and 33. Claim 22 is canceled without prejudice. As discussed below, these amendments are fully supported by the specification as originally filed and therefore no new matter is added. Upon entry of the amendments, claims 18-21 and 23-33 are pending.

In light of the amendments and remarks as set forth herein, Applicants respectfully request withdrawal of the claim rejections and consideration of pending claims for the patentability.

Discussion of Claim Amendments

Support for the amendment to claim 18 can be found in, for example, from page 6, lines 4-5 of the specification as filed.

The features related to the monoclonal antibody in claim 21 can be found from Figures 2 and 4 and their related descriptions of the subject application. The specific language is supported by Example 1 of the specification. In addition, the citation in claim 21 that the method identifies the presence of nephritis at an early stage before formation of glomerular crescent, has been described from page 1, line 27 (the last line) to page 2, line 5 of the specification.

Claims 20 and 28 are amended to provide full description of the acronym.

Support for the amendment to claim 25 and new claims 32 and 33 can be found from, for example, Table 1. Staining Procedure, which is disclosed in page 12, Example 1, and Figures 2 and 4 of the specification.

As such, the claim amendments in this response are fully supported and do not constitute any new matter. Applicants respectfully request entry of the amendments.

Claim rejections under 25 U.S.C. 112 (enablement)

Claims 25 and 29 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. In these rejections, the Examiner relied on the teaching of Johansson et al. (J. Biol. Chem. 267: 24533, 1992) that NC1 is present in the normal glomerular basement membrane. Based on this teaching, the Examiner concluded that the cited antibody in claims 25 and 29 would bind to NC1 of the normal kidney as well as the kidney with nephritis.

Based on this conclusion, the Examiner asserted that the user of the claimed method would not be able to discern the nephritis condition. However, as discussed below, this assertion of the Examiner is not accurate.

The antibody of claims 25 and 29 exhibits substantially more binding to glomeruli of macaques in which nephritis has been induced by anti-GBM antibody than to glomeruli of normal macaques. The selection of such a monoclonal antibody is exemplified in Example 1 of the specification as filed. The specification as originally filed provides experimental evidence showing the binding of antibodies meeting the recited limitation to both normal and anti-GBM antibody induced nephritic kidneys in Figures 2 and 4. For example, in one embodiment as presented in Figure 2, the anti-NC1 monoclonal antibody shows a significantly and noticeably more binding to the nephritis model kidney (lower panel) than the normal control kidney (upper panel). Such noticeably distinctive binding of the cited antibody to the different samples would allow the user to readily identify the sample under condition of nephritis. Accordingly, Applicants respectfully submit that claims 25 and 29 are in compliance with the enablement requirement, and therefore request withdrawal of the rejections.

Claim rejections under 25 U.S.C. 112 (indefiniteness)

Claims 20 and 28 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. More particularly, claims 20 and 28 were rejected due to the acronym "GBM" and "AB", respectively. The full definition of these acronyms is now cited in the claims as set forth above. Therefore, claims 20 and 28 are now in compliance with 35 U.S.C. 112, second paragraph. Applicants respectfully request reconsideration of claims 20 and 28.

Claim rejections under 102(b)

The Examiner rejected claims 21, 23-27, 30, and 31 under 35 U.S.C. 102(b) as allegedly anticipated by Yokoyama et al. (Cell 35: 40, 2003). Applicants respectfully traverse these rejections.

Anticipation under Section 102 can be found only if a reference shows exactly what is claimed. *Titanium Metals Corp. v. Banner, 778 F.2d 775 (Fed. Cir. 1985).* More particularly, a finding of anticipation requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention. Yokoyama reference, however, does not disclose every feature

of claim 21. For example, the anti NC1 antibody disclosed in Yokoyama is not a monoclonal antibody, but a polyclonal antibody. As well known in the art, the monoclonal antibody is produced only via an *in-vitro* method (e.g. production from a hybridoma cell line), otherwise it cannot function as a monoclonal antibody. Yokoyama described in the section of 2) Composition of the kit (*See* the last section of page 2 of Yokoyama) that the anti NC1 antibody is derived via an *in-vivo* method using animal (i.e. rabbit), which indicates that the antibody is polyclonal. The use of monoclonal antibody is a critical component of Applicants' invention. Figure 2 shows results generated with the monoclonal anti NC1 antibody as recited in claim 21. The signal obtained from the anti-GMB nephritis (lower panel) is significantly higher than the one from the control kidney (upper panel). In contrast, the anti NC1 polyclonal antibody tested in Figures 3-1 and 3-2 stained both kidneys from a nephritis monkey and a normal monkey with equal sensitivity. These results clearly prove that Yokoyama method does not and cannot teach the method of claim 21.

In addition, the claims recite "identifying presence of nephritis in a mammal at an early stage before formation of glomerular crescent." In contrast, Yokoyama expressly stated that the method would be able to detect nephritis only after formation of a lesion, such as glomerular crescent. *See* page 6, lines 28-29 of Yokoyama. The claimed method, however, detects the presence of nephritis even before formation of glomerular crescent, by using the monoclonal antibodies recited in the claims. Therefore, Yokoyama fails to teach this feature of claim 21 as well.

As noted, Yokoyama fails to teach at least some features of claim 21 and therefore does not anticipate claim 21. Accordingly, Applicants respectfully request withdrawal of the rejection to claim 21 under 35 U.S.C. 102(b). As to claims 23-27, 30, and 31, they incorporate all the features of claim 21, through their dependencies from claim 21. Therefore, they are also patentable over Yokoyama for at least the same reasons that claim 21 is patentable. Reconsideration of these dependent claims is respectfully requested.

Claim rejections under 103(a) over Yokoyama, Campbell, Cosmo Bio Co. Ltd. catalog and letter, Sugihara, and Johansson

Clams 21-31 were rejected under 35 U.S.C. 103(a) as being unpatentable over Yokoyama, if necessary further in view of Campbell, Cosmo Bio Co. Ltd. catalog and letter, Sugihara *et al.*

(J. Pathol 178: 352, 1996), and Johansson et al. *id.* Applicants respectfully disagree with these rejections.

As correctly cited by the Examiner, Johansson teaches that NC1 is present not only in a kidney with nephritis but also in a normal, health kidney. Johansson even provided monoclonal antibodies against NC1 that can be used in affinity chromatography and isolate NC1 proteins from the normal kidney tissues. *See* Abstract of Johansson. These disclosures of Johansson would not teach or suggest the claimed method to one of ordinary skill in the art, but rather **teach away** from using a monoclonal NC1 antibody to identify nephritis, especially at an early stage. The Examiner himself concluded in the enablement rejection at page 2, line 20 to page 3, line 3 of the Office Action that the Johansson reference would lead one having ordinary skill in the art to conclude that it would not be possible to practice the claimed invention. Unexpectedly, as described by Applicants in Figures 2 and 4 and the accompanying text, monoclonal antibodies can be identified that bind to nephritis glomeruli but not to normal glomeruli. Based on Johansson, one having ordinary skill in the art would never expect these successful results.

Like Johansson, Sugihara also disclosed that type IV collagen is one of the major structural components of basement membranes and fails to teach a monoclonal NC1 antibody that can specifically recognize a kidney tissue with nephritis. *See* the first two lines, second paragraph of Introduction of Sugihara. As such, the teachings of Johansson and Sugihara would not render the claimed method obvious.

Despite the teaching-away by the prior art as noted above, if the combination of the cited references, e.g. the combination of Yokoyama, Campbell and information present by Cosmo Bio Co. Ltd. at best, would be attempted, it would still fail to achieve the claimed method. Nothing in any of these references would provide any reason to expect that monoclonal antibodies that bind to nephritis glomeruli but not normal glomeruli could be identified. As noted, Yokoyama fails to teach a method comprising a monoclonal anti NC1 antibody, which is configured to have a substantially higher affinity to a sample under condition of nephritis than a normal sample. Further, Yokoyama fails to disclose a method to identify the presence of nephritis at an early stage, which is before formation of glomerular crescent. Campbell merely discloses how to produce a monoclonal antibody, but it does not cure the deficiency of Yokoyama. Cosmo Bio Co. Ltd. catalogue and letter merely recites "preparation of nephritis model" or "studying anti glomerular basement membrane nephritis" for the anti NC1 antibody or its kit. However, there

is no disclosure regarding how to detect nephritis using a monoclonal anti NC1 antibody and much less such detection at an early stage of nephritis. Rest of the catalog and letter recites literally a name of antibody, storage condition of an antibody or kit, and some other information that is irrelevant to a nephritis detection method. Therefore, even if the teachings of Yokoyama, Campbell and Cosmo Bio Co. Ltd., further with Sugihara and Johansson, would be properly combined, which they are not, it still fails to disclose the claimed method of claim 21.

As discussed above, the cited references do not teach or suggest the claimed method and, moreover teach away from practicing such method. Therefore, claim 21 is not obvious but patentable over the cited references. Applicants respectfully request withdrawal of the claim rejection under 35 U.S.C. 103(a). Claims 23-31 are dependent from claim 21, and therefore are also in condition of allowability in light of claim 21 being allowable as well as for their own features. Applicants respectfully request to the Examiner reconsidering these dependent claims. Claim 22 is canceled without prejudice, so that the rejection to this claim is moot.

Claim rejections under 103(a) over Yokoyama, Oftshun, and Sugihara

Clams 18-20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Yokoyama, together with Oftshun *et al.* (US 5871649) and Sugihara. However, as described below, these references provide no reason to expect that an antibody exhibiting binding to nephritis glomeruli but not normal glomeruli could be obtained. Thus, there would be no reasonable expectation of success in achieving the invention claimed. Without this reasonable expectation of success the claimed invention cannot be considered obvious.

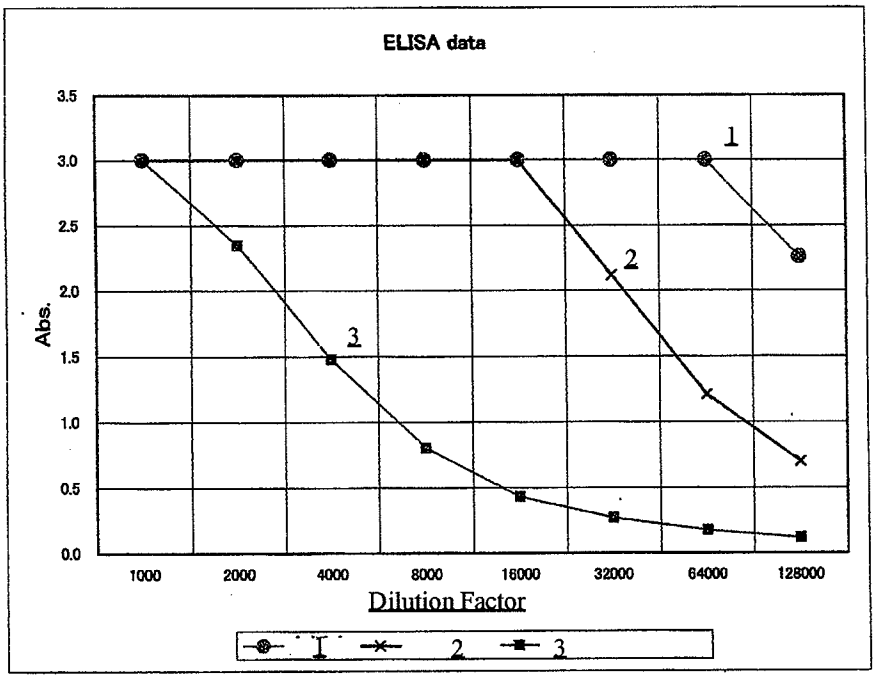
Claim 18 now recites, among others, an apparatus for removing an anti-noncollagenous domain of collagen (NC1) antibody and NC1 from blood, comprising an affinity column wherein an the anti NC1 monoclonal antibody similar to that recited in Claim 21 is immobilized for dialyzing blood to remove NC1 in the blood; and an affinity column wherein an the NC1 is immobilized for dialyzing the blood to remove anti NC1 antibody in the blood, wherein the NC1 is able to bind the anti NC1 monoclonal antibody. As noted, Yokoyama does not teach a monoclonal NC1 antibody that exhibits more binding under condition of nephritis than to a normal sample. Further, Yokoyama only teaches a measurement of NC1 and its antibody to detect nephritis but never discloses or suggests the removal of NC1 and NC1 antibody as cited in

claim 18. This deficiency of Yokoyama is also correctly cited in the Office Action in page 7, lines 1-3.

In addition, Sugihara does not disclose either the recited monoclonal NC1 antibody of claim 18 nor any concept or apparatus to remove NC1 and NC1 antibody from a mammal; instead it merely teaches how to induce a nephritis model in rat by injecting NC1 peptide or NC1 antibody. Therefore, Sugihara does not remedy the deficiency of Yokoyama. Oftshun is related to a device and method for removing target molecules in plasma. This reference, does not mention NC1 and its antibody at all and much less the removal of NC1 and the antibody using an affinity column comprising NC1 and anti NC1 monoclonal antibody. Oftshun merely teaches removal of autoantibodies from a patient of Goodpasture's Disease; however, it does not teach expressly what needs to be removed (i.e. NC1 and NC1 antibody) and how to remove them. As such, even if Oftshun's teaching would be combined with the disclosures of Yokoyama and Sugihara, which they are not, it still fails to disclose the claimed apparatus as in claim 18.

Based on the teachings of the references there would be absolutely no basis to expect successful results with the claimed invention. Accordingly, *no prima facie* showing of obviousness can be established based on these references.

Furthermore, the claimed apparatus of claim 18 shows **unexpectedly improved ability** to remove both NC1 antigen and its antibody from a biological sample. As readily disclosed in page 6, lines 8-13 and Examples 2 in page 9 of the specification, the apparatus of claim 18 removes 50% or more of NC1 and NC1 antibody from urine and blood samples, which is substantially more efficient than a conventional dialysis method. To further support this, Applicants provide a separate set of experiment data quantitatively showing the difference in the NC1 antibody level before and after the application of the claimed apparatus.



1. Total blood collected
2. Purifieid Antibody
3. Affinity filtrate

As seen above, when the blood sample obtained form a nephritis model guinea pig was treated with an affinity column according to claim 18, the absorbance indicating the level of NC1 antibody becomes significantly decreased as compared to no filtration (i.e. total blood collected). Such efficient removal of NC1 antibody as well as NC1 is not expected in light of the references, which fail to teach the claimed apparatus individually or in combination. In light of these unexpected results, any *prima facie* showing of obviousness would be overcome. Accordingly, Applicants respectively request withdrawal of claim rejection and reconsideration of claim 18 and its dependent claims 19 and 20, which incorporate all the feature of claim 18, thereby being allowable in light of claim 18 being allowable.

Allowability of New Claims 32 and 33

Claims 32 and 33 are newly added and these claims recite the methods as presented in Staining Procedures (Table 1) in page 12, Example 1, and Figures 2 and 4 of the specification as originally filed. Therefore these new claims are fully supported and do not add any new matter. The methods cited in claims 32 and 33 are further specified from what is disclosed in claim 21. As noted above, the subject method of claim 21 is patentable over the cited references; therefore

the methods of claims 32 and 33, which incorporate all the features of claim 21 and the additional features, should also be patentable. Applicants respectfully request the Examiner's consideration of the new claims for the patentability.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of Applicants' foregoing Amendments and Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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